CLINICAL VIGNETTE

Hereditary Diffuse Gastric Cancer

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Case Report

A 54-year-old male presented for evaluation after being found positive for the E-cadherin (CDH1) gene mutation. He has a significant family history of multiple cancers. The patient's father had gastric cancer at the age of 35, one brother with a history of throat cancer, and one sister with non-Hodgkin lymphoma and breast cancer diagnosed in her 50s. He has another sister diagnosed with gastric cancer at the age of 53, who is also CDH1 positive. This same sister also has a history of breast cancer. He has a nephew with gastric cancer diagnosed at the age of 31. The patient denies any symptoms of abdominal pain, change in his appetite, unintentional weight loss, nausea, or vomiting. He previously underwent normal colonoscopy and upper endoscopy three years prior to this presentation. The upper endoscopy included multiple biopsies, which were normal as well. He underwent prior endoscopy four years ago with unremarkable biopsies, as well as colonoscopy six years ago with removal of three tubular adenomas. He has a past medical history of asthma and past surgical history of vasectomy.

On physical exam he had a heart rate of 94, blood pressure of 125/86, and weight of 168 pounds. The exam was unrevealing including a normal abdominal examination. Repeat endoscopy was normal including multiple normal biopsies using the gastric mapping protocol. Two small tubular adenomas were removed during the colonoscopy.

The patient wants to know the recommendations regarding the further management of his condition.

Discussion

Hereditary diffuse gastric cancer is an extremely aggressive cancer that is inherited as an autosomal dominant trait with a very high penetrance. The result of the CDH1 gene mutation is loss of expression of E-cadherin, which is a cell adhesion molecule. It carries a high risk of gastric cancer, greater than 80% overall, in both men and women by the age of 80.[1] More specifically, the risk in men is as high as 70% and as high as 80% in women.[2,3] The average age of diagnosis of gastric cancer in these patients is 38. There is also a 60% risk of developing lobular breast cancer by age 80.[1]

There are various guidelines and criteria that have been proposed for determining who should be tested for CDH1 gene mutations. The original guidelines were put forth by the Gastric Cancer Linkage Consortium in 2000. Subsequently, modified guidelines were proposed by the British Columbia Cancer Agency Hereditary Diffuse Gastric Cancer Program. The most recent guidelines for CDH1 mutation testing come from the Gastric Cancer Linkage Consortium in 2010. Testing should occur in family members when there is a history of two gastric cancers in one family as well as one of the following:

- One with diffuse gastric cancer under the age of 50;
- Three cases of diffuse gastric cancer at any age in first or second degree relatives;
- One case of diffuse gastric cancer under the age of 40; or
- Diffuse gastric cancer and lobular breast cancer (one diagnosed under age 50).[1]

Testing should also occur in cases of gastric cancer where signet ring cells are detected.[4] The best testing method uses a blood sample[5] and should generally start when patients are between 16 and 18 years old.[6]

Gastric cancer in patients with HDGC tend to be deeper cancers resulting in difficult diagnosis. They lie beneath the epithelium and only manifest with mucosal abnormalities when the disease is advanced.[7,8] Therefore, there are no reliable early detection or screening methods available. Careful endoscopy should be performed using a high-definition endoscope with multiple targeted and random biopsies.[9,10] However, even with these methods detection rates are still only about 9% with serial endoscopy.[11] PET scanning has been examined in one small study but is not reliable enough to be used as a screening or surveillance modality.

In patients with a confirmed CDH1 gene mutation leading to loss of function of the E-cadherin protein and a family history of gastric cancer, prophylactic total gastrectomy should be strongly considered. Gastrectomy should be considered in the early 20s or five years younger than the age of the youngest family member to develop gastric cancer.[12] In patients who decline prophylactic gastrectomy, yearly endoscopic surveillance should be performed. However, patients must be informed of the potential shortcomings of this method. Female patients should also undergo earlier and more stringent

breast cancer screenings. All patients with the CDH1 gene mutation should also be referred for genetic counseling.

Clinical Case Follow-up

Based on our patient's family history of gastric cancer and his positive testing for the CDH1 gene mutation, we discussed prophylactic total gastrectomy. He was informed of the up to 80% risk of developing gastric cancer by the age of 80. He was also referred to discuss this with a genetic counselor, oncologist, and surgeon. The consensus recommendation was for the patient to undergo prophylactic total gastrectomy. However, he has declined this procedure despite the recommendations. He currently continues to undergo yearly surveillance endoscopy with numerous biopsies.

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